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A1

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 83306638.4

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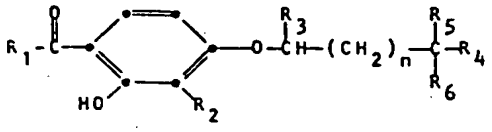
(54) Leukotriene antagonists.

(57) Novel alkane derivatives of the formula (I)



I

or a pharmaceutically acceptable salt thereof, wherein:
R_1 is hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, or phenyl;
R_2 is hydrogen, C_1-C_6 alkyl, or C_2-C_6 alkenyl;
R_3 is hydrogen, C_1-C_{10} alkyl, phenyl, C_1-C_{10} alkyl-substituted phenyl, biphenyl, or benzylphenyl;
R_4 is $-COOR_7$, $-CONR_8R_9$, $-CONHOH$, $-NR_8R_9$, $-SC(=NH)NH_2$, cyano, cyanothio,

where R_7 is hydrogen or C_1-C_4 alkyl,
R_8 and R_9 are each independently hydrogen, C_1-C_3 alkyl, or when taken together with the nitrogen atom form a morpholine or N-methyl piperazine ring,
R is hydrogen, C_1-C_4 alkyl, or $-CH_2COOR_7$, and p is 0, 1, or 2;
R_5 and R_6 are each independently hydrogen or C_1-C_3 alkyl; and n is 0-10 are leukotriene antagonists.

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A/-124 B 69/66 C2 B4 C2

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C 07 C 149/24, C 07 C 149/233

No	références, formules, pages à photocopier, etc	No	classement
		1.	C07D257/04D2C3
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5	p 25, 26, 27	5	INF 124 B 69/76 B2A
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8	p 35-36	8	INF 124 B65 G2 CV
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PIÈCES A RETOURNER A
S. A. Fedit - Loriot
(Cabinet Guerbilsky)

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rated and the aqueous phase was extracted with 50 ml. of methylene chloride. The combined organic layers were washed once with water, once with a saturated sodium chloride solution, dried over sodium sulfate, and concentrated in vacuo to give 14 g. of a pale yellow liquid, which was identified as methyl 6-bromo-2,2-dimethylhexanoate by NMR and IR.

B. Preparation of methyl 6-(4-acetyl-3-hydroxy-2-propylphenoxy)-2,2-dimethylhexanoate.

Following the procedure of Example 15, 2.5 g. of methyl 6-bromo-2,2-dimethylhexanoate, 1.46 g. of potassium carbonate, a catalytic amount of potassium iodide, and 2.14 g. of 2,4-dihydroxy-3-propylacetophenone were reacted to give 2.96 g. of the title product as a brown oil. IR, NMR.

Example 45

6-(4-Acetyl-3-hydroxy-2-propylphenoxy)-2,2-dimethylhexanoic acid

A solution of 1.1 g. of methyl 6-(4-acetyl-3-hydroxy-2-propylphenoxy)-2,2-dimethylhexanoate and 2.6 g. of lithium iodide in 50 ml. of collidine was heated to 100°C under a nitrogen blanket for about 46 hours. The reaction mixture was then added to ice. After making the solution acidic with hydrochloric acid, the solution was extracted with ether. The ether phase was washed three times with a 10% sodium bicarbonate solution. The ether solution was then further washed with a dilute hydrochloric acid solution, water,

with 4.86 g. of 5-bromovaleronitrile according to the procedure in Example 21. The reaction afforded 8.2 g. of the nitrile intermediate of the title compound. This nitrile intermediate was then converted to the tetrazole following the procedure of Example 8 giving 1.2 g. of the title compound, m.p. about 114-115°C.

Analysis: $C_{21}H_{24}N_4O_3$;
Calc.: C, 66.30; H, 6.36;
Found: C, 66.15; H, 6.36.

Example 44

Methyl 6-(4-acetyl-3-hydroxy-2-propylphenoxy)-2,2-dimethylhexanoate

A. Preparation of methyl 6-bromo-2,2-dimethylhexanoate.

To a solution of 5.0 g. of dry diisopropylamine in 60 ml. of dry tetrahydrofuran at -70°C were added dropwise via a syringe 32.6 ml. of a 1.5M solution of n-butyllithium in hexane. After stirring for about 20 minutes at -70°C, 6.0 g. of methyl isobutyrate were added and the reaction mixture allowed to stir at -70°C for about 40 minutes. A solution of 15.76 g. of 1,4-dibromobutane in a small volume of tetrahydrofuran was then added to the reaction mixture. The reaction mixture was slowly brought to room temperature over a period of about three hours. The reaction was quenched with 2.5 ml. of methanol. Fifty ml. of methylene chloride were added followed by the addition of 50 ml. of 0.5N sodium hydroxide. The layers were sepa-

chloride). The appropriate fractions were pooled and evaporated to an oil. Crystallization from ethyl acetate/hexane afforded 1.5 g. of the title product, m.p. about 72-75°C.

Analysis: $C_{18}H_{26}N_4O_3$;
Calc.: C, 62.41; H, 7.57; N, 16.17;
Found: C, 62.14; H, 7.40; N, 15.91.

Example 53

Alternate preparation of 5-(4-acetyl-3-hydroxy-2-propylphenoxy)pentanoic acid

The title product was prepared by heating 15.0 g. of 5-(4-acetyl-3-hydroxy-2-propylphenoxy)pentane nitrile to reflux for six hours in 300 ml. of 2B ethanol and 40 ml. of 25% aqueous sodium hydroxide. The solution was evaporated to dryness and the residue was partitioned between diethyl ether and dilute sodium hydroxide solution. The aqueous layer was separated and acidified. The aqueous layer was extracted with ether. The ether extract was dried over sodium sulfate and evaporated to dryness. The residue was triturated with hexane and filtered to give 11 g. of the title product.

Example 54

Ethyl 5-(4-acetyl-3-hydroxy-2-propylphenoxy)-pentanoate

Eleven grams of 5-(4-acetyl-3-hydroxy-2-propylphenoxy)pentanoic acid were dissolved in 200 ml. of absolute ethanol. With stirring, 1 ml. of sulfuric acid was added and the reaction was stirred overnight.

and a saturated sodium chloride solution. Evaporating the ether layer to dryness gave 1.03 g. of the title product, M^+ = 336; NMR.

Example 46

Methyl 6-(4-acetyl-3-hydroxyphenoxy)-2,2-dimethylhexanoate

Following the procedure of Example 44, 2.5 g. of methyl 6-bromo-2,2-dimethylhexanoate, 1.46 g. of potassium carbonate, a catalytic amount of potassium icdide, and 1.67 g. of 2,4-dihydroxyacetophenone were reacted in 125 ml. of acetone giving 2.3 g. of the title product as an oil. M^+ = 308; NMR.

Example 47

6-(4-Acetyl-3-hydroxyphenoxy)-2,2-dimethyl-hexanoic acid

Following the procedure of Example 45, 1.0 g. of methyl 6-(4-acetyl-3-hydroxyphenoxy)-2,2-dimethyl-hexanoate was hydrolyzed to give 0.86 g. of the title product. M^+ = 294; NMR.

Example 48

6-(4-Acetyl-3-hydroxy-2-propylphenoxy)-nonanoic acid

Following the procedures of Examples 15E and 15F, 1.18 g. of methyl 6-bromo-nonanoate and 0.91 g. of 2,4-dihydroxy-3-propylacetophenone were reacted in the presence of 0.65 g. of potassium carbonate in 40 ml. of acetone. Hydrolysis of the ester intermediate with

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EUROPEAN SEARCH REPORT

Application number

EP 83306638.4

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. ³)
A	CH - A5 - 599 184 (SANDOZ) * Claim 1 * --	1	C 07 D 257/04 C 07 C 59/90 C 07 C 69/738 C 07 C 103/178 C 07 C 121/38 C 07 C 51/00 C 07 C 67/00 C 07 C 102/00 C 07 C 120/00 C 07 C 149/24 C 07 C 149/233 A 61 K 31/41 A 61 K 31/12
A,P	US - A - 4 372 953 (UCHIDA) * Formula 1 * --	1	
A	US - A - 3 649 637 (HOWES) * Formula VI * --	1	
A	DE - A - 2 250 327 (FOURNIER) * Claims 1,8; pages 7-11 * --	1	
A	CHEMICAL ABSTRACTS, vol. 91, no. 7, August 13, 1979, Columbus, Ohio, USA SHUKLA, J.S., AHMAD, I.; Saxena, Shradha "Synthesis and antiinflammatory activity of some substituted tetrazoles" page 701, column 1, abstract-no. 56 921x & Indian J. Pharm. Sci. 1979, 41(2), 70-1 ----	1	

TECHNICAL FIELDS SEARCHED (Int. Cl. ³)

C 07 D 257/00
C 07 C 59/00
C 07 C 69/00
C 07 C 103/00
C 07 C 121/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	16-01-1984	HAMMER

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
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P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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The solvent was evaporated in vacuo and the residue partitioned between ethyl acetate and dilute potassium carbonate solution. The ethyl acetate was separated, dried, and evaporated to give 9.9 g. of the title product, $M^+ = 322$.

Analysis: $C_{18}H_{26}O_5$;
Calc.: C, 67.06; H, 8.13;
Found: C, 66.43; H, 7.03.

Example 55

5-(4-Acetyl-3-hydroxy-2-propylphenoxy)pentanoic acid amide

The acid chloride of 5-(4-acetyl-3-hydroxy-2-propylphenoxy)pentanoic acid was prepared by dissolving 9.3 g. of the acid in 150 ml. of methylene chloride followed by the addition of ten drops of dimethylformamide and 5.22 ml. of oxalyl chloride. After stirring at room temperature for one hour, the solvent was evaporated in vacuo. The residue was dissolved in benzene and evaporated in vacuo. The resulting acid chloride was dissolved in 100 ml. of methylene chloride and the solution was divided in half. One-half of the acid chloride solution was used in Example 56; the other half (50 ml.) of the acid chloride solution was added dropwise to 200 ml. of liquid ammonia. After stirring overnight, the solvent was evaporated and the residue was partitioned between dilute hydrochloric acid and ethyl acetate. The ethyl acetate solution was separated, washed once with dilute aqueous potassium carbonate, dried over sodium sulfate, filtered and evaporated to dryness. Crystallization from methylene chloride/hexane resulted in a total of 2.8 g. (two crops) of the title product, m.p. about 108-110°C.